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PROTECTION AGAINST IONIZING RADIATION

X-irradiated Monkeys Receiving Preirradiation Prophylaxis and Postirradiation Therapy

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FOREWORD

This report was prepared in the Bionucleonics Department* and the Veterinary Services Branch† by the following personnel:

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ABSTRACT

In this study, postirradiation symptomatic therapy of the radiation syndrome has been utilized to provide significant extension of survival time, compared to irradiated controls, of *Macaca mulatta* primates exposed to a total dose of 900 r. Further, the therapeutic regimen has been successfully combined with chemical radioprotectants to enhance survival time in a third group of animals. This combined treatment is more effective than the therapy alone. The overall clinical condition of these animals is far superior to that of the untreated irradiated animals. Pathologic studies of the deceased animals indicate that the two major causes of death were bone marrow failure and severe lymphoid atrophy. The protective chemical treatment is in itself a combination of different mechanisms of radioprotection, routes of administration, and sites and rates of absorption of the drugs.

This technical documentary report has been reviewed and is approved.

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1. INTRODUCTION

In previous studies in this laboratory it has been shown that the radioprotection conferred by certain sulfhydryl-containing chemicals can be enhanced in rats, either additively or synergistically by other compounds (5). Similar studies have also been effected in monkeys, and the findings on the primate substantiate those found for the rodent (4).

At the present "state-of-the-art" of chemical radioprotection, it would seem that, although effective radiation dose reduction can be achieved, a supralethally irradiated animal will still sustain appreciable damage. Some, if not all, of the clinical sequelae of radiation sickness thus will be manifested. Clinical treatment of chemically protected animals therefore becomes essential if the dose-reducing advantages of the radioprotective chemicals are to be optimized.

This report details the first study accomplished at this laboratory in which radioprotective prophylaxis has been followed by medical treatment after the irradiation has been administered. Eight monkeys were given the best chemical treatment available in this laboratory (3, 4, 5), after which they received 950 r of x-rays (= 100%, lethal within 15 days at this laboratory, and approximately that elsewhere (2)). The same animals received medical treatment as suggested by clinical indices. Results indicate that the combination of treatments significantly increased the life-span of all survivors, the longest lived succumbing at 618 days postexposure.

2. MATERIAL AND METHODS

The monkeys used were of the *Macaca mulatta* strain of rhesus monkey and ranged from 4.5 to 6.5 lb. The eight treated animals were chosen at random from a larger group of healthy animals. In this selection, no distinctions were made on the basis of sex; there were two females and six males. Ten other animals (four females and six males) were irradiated at 950 r as controls: four no-treatment controls, and six postirradiation therapy controls.

The whole-body x-irradiations were performed with a Picker x-ray machine at 250 kvp, 15 ma., with 1 mm. Al and 0.25 mm. Cu added filtration. The dose rate was 18 to 20 r/min.; the exposure cage was rotated at 15 r.p.m. S,2-aminoethylisothiuronium dibromide (AET) was synthesized and purified in this laboratory by the method of Shapiro (7).

All protected animals received AET-dibromide (75 mg./kg. body weight) plus cysteine-HCl (225 mg./kg. body weight) intravenously, 60 minutes prior to irradiation; AET-dibromide (150 mg./kg. body weight) plus cysteine-HCl (150 mg./kg. body weight) orally, 15 minutes before irradiation, and Nembutal (8 to 10 mg./lb. body weight) intravenously, 15 minutes prior to irradiation.

Intravenous doses of AET and cysteine were prepared by weighing the appropriate amount of each into a common vessel, and neutralizing them with 2.5 normal NaOH to a final pH of

The work was carried out at the Radiological Laboratory of the University of Texas and the United States Air Force Aeromedical Field.

7.2 to 7.4. Samples were diluted to 10 ml. with distilled water and administered 60 minutes before irradiation.

Oral doses of AET and cysteine were prepared in a similar manner, neutralized together with 2.5 normal NaOH to a pH of 7.2 to 7.4, diluted to 8 to 10 ml. with 0.5 M phosphate buffer, and gavaged 15 minutes before irradiation.

Nembutal was administered intravenously 15 minutes before irradiation at a dose of 8 to 10 mg./lb. body weight. A minimum dose was used to achieve anesthesia, checking by the "eyelid-reflex" method. As a result, the entire calculated dose was sometimes not used.

Hematologic examinations were accomplished on blood drawn by femoral puncture; the methods specified by Wintrobe (9) were used for counting and for other determinations.

Bacteriologic and parasitologic examinations were effected on blood and feces both before and after irradiation. Samples for parasitology were examined by the ether concentration method; stool bacteriologic samples were examined by the standard "three-media" technic and then by tetrathionate enrichment; blood bacteriologic samples were collected on 1-oz. agar slants using tryptose-glucose broth, and then plated by standard technics. To aid in the case of antibiotics, positive blood cultures were tested for sensitivity to various drugs by using the paper disc method.

Temperatures were obtained rectally in this laboratory. 102° F. is a normal mean value for this strain of monkey.

TABLE I

Survival of monkeys irradiated with 800 r of x-rays

Animal No.	Survival time (days)	Experimental treatment
Group I		
118C	9	None
134F	9	
74E	9	
197J	32	
Group II		
92E	11	Postexposure therapy as indicated by individual symptoms
93E	11	
71E	12	
31E	13	
78E	15	
114E	82	
Group III		
66K	14	All animals received the following treatments (per kilogram body weight):
98E	24	
60E	29	
55F	32	60 minutes pre-exposure: intravenous injection of AET-di-HBr (75 mg. plus cysteine-HCl (25 mg.) in neutralized aqueous solution
31E	60	
125E	80	
95B	250	
48K	618	15 minutes pre-exposure: AET-di-HBr (150 mg.) plus cysteine-HCl (50 mg.) administered orally as above. Intramuscular (8.10 mg.) administered concurrently
		Postexposure: Therapy as indicated by individual symptoms

Water intake was obtained by calculating the amount consumed from a 500-ml. bottle of water given to each animal daily. Food consumption (in calories) was calculated by estimating the unconsumed portion of the amount given approximately 16 hours after feeding.

The survival time, calculated in days, was used in comparing the treated animals with the irradiated-therapy controls, and separately with the irradiated controls that received no treatment. The Mann-Whitney "U" Test was used, as expounded by Siegel [8]. Mortality data were arranged in contingency tables and the probabilities were calculated by Fisher's Exact Method at the 30-day point.

3. RESULTS

Table I summarizes the longevity of the eight animals that were treated before and after irradiation (group III); control animals that were given therapy after irradiation (group II); and the four irradiated control animals that received no treatment (group I). Mean survival time for group I was 10 days; group II, 21 days; group III, 135 days.

Figure 1 shows weight and temperature changes for the first 30-day period postirradia-

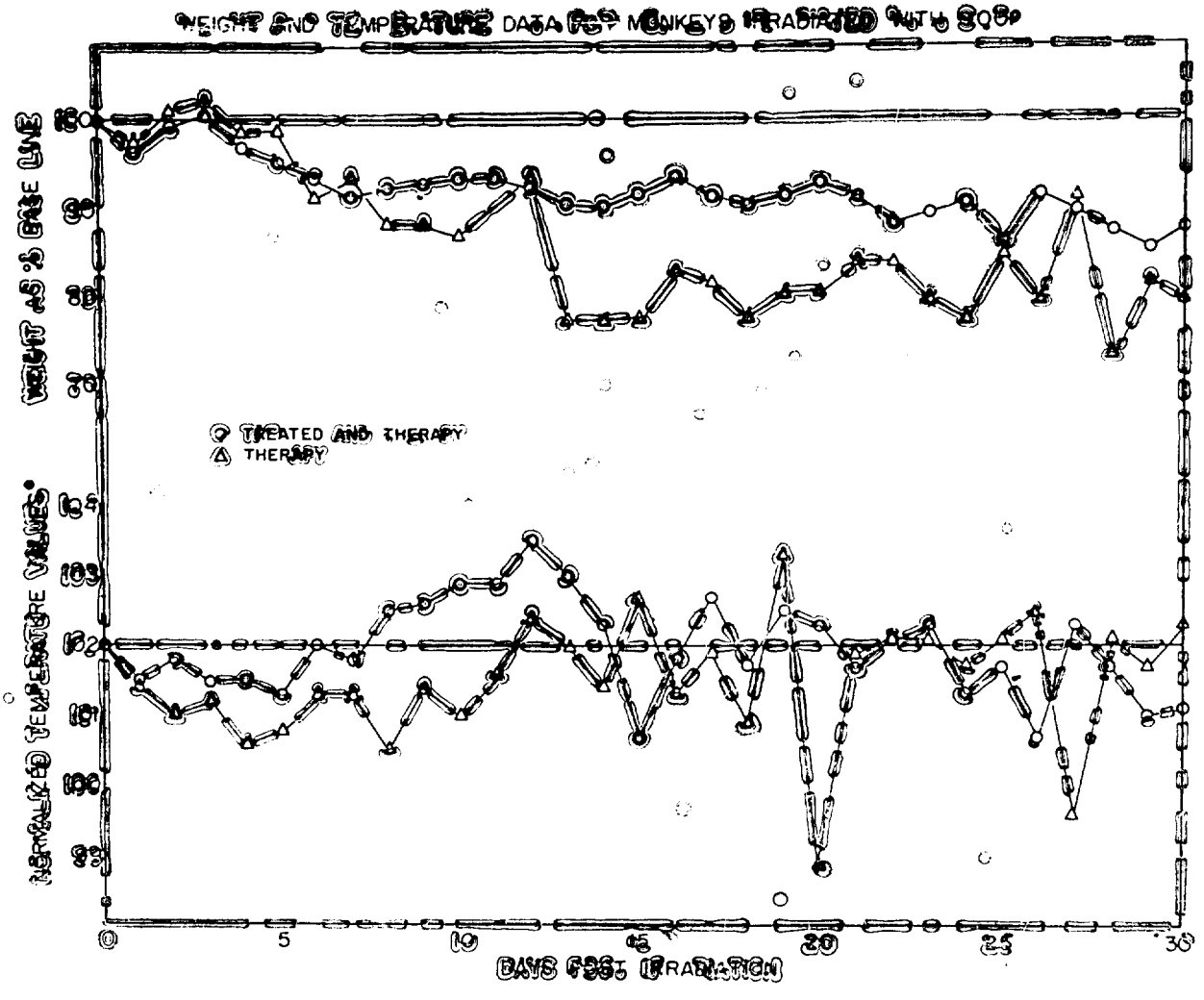

FIGURE 1

Postirradiation changes in body weight and temperature for groups II and III.

tion. These values are means for the animals which were alive when the sample was taken; weights have been presented as percentages of the baseline values before irradiation which, in turn, have been normalized to the normal value for the rhesus monkey in this colony. The animals pretreated with the chemical protectants (group III) maintain their weight better than those that received supportive treatment only (group II).

Variations in temperature are less dramatic; however, animals in group III also maintain their body temperature better during the early and late stages of the 30-day period, and there is less fluctuation than in group II. Figure 2 is a hemogram which presents four peripheral blood parameters for groups II and III. The values are means for the animals alive at the time of the sampling. There are very few differences in the two groups. The

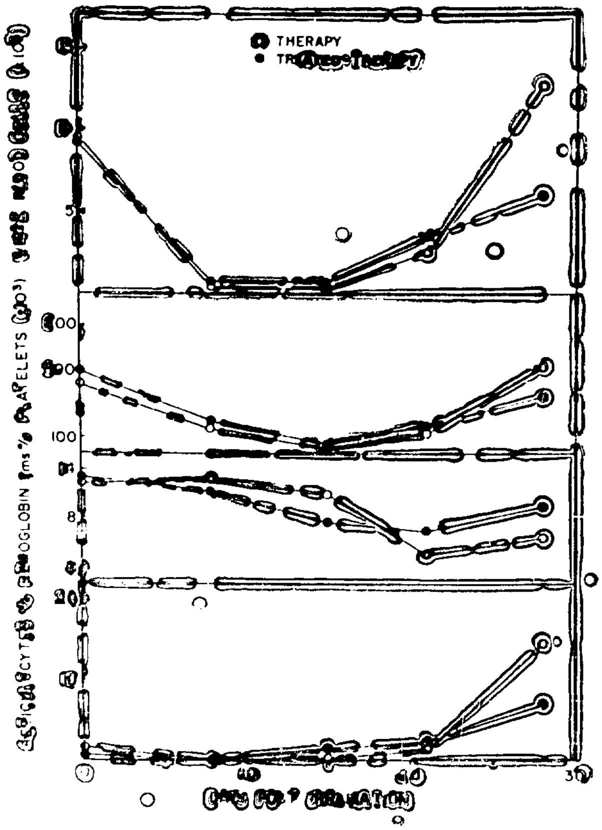

FIGURE 2

Hemogram showing postirradiation changes in peripheral blood values for groups II and III.

TABLE II

Statistical probabilities for the survival of monkeys

	Fisher's Exact Test (Number dead or alive)	Mann-Whitney "U" Test (days until death)
Group I* vs. Group II†	.500	.033 > P > .0[illegible]
Group I* vs. Group III‡	.[illegible]	.002
Group II† vs. Group III‡	.2[illegible]	.02[illegible]

*Irradiated control animals.
†Immediate therapy control animals.
‡Protection-immediate therapy animals.

white blood cell count is higher for group II, and, although to less extent, platelets and reticulocytes are also higher. In group III, hemoglobins are somewhat higher during the last week.

Table II shows the results obtained by applying Fisher's Exact Test and the Mann-Whitney "U" Test to these data. None of the mortality data are considered significant (requirements P<.05); however, there is significant improvement in survival times in all cases.

Table III summarizes the remainder of the clinical history of group II before and after irradiation. The animals have been listed in order of increasing longevity. The numbers in parentheses indicate the first day on which cultures were positive, and the days on which drugs were administered. It will be noted that animals receiving the most treatment lived the longest. Clinically, however, these animals showed the most symptoms since symptoms were the basis for therapy.

As the general condition of the animals of group I was very poor, they were delineated quite easily from the treated groups at the end of the first week. Symptoms included

TABLE III

Clinical summary for group II

Animal No.	Preirradiation: Stool: Ova and parasites	Preirradiation: Stool: Enteric pathogens	Preirradiation: Blood: Pathogens	Preirradiation: Blood: Hematology	Postirradiation: Stool: Ova and parasites	Postirradiation: Stool: Enteric pathogens	Postirradiation: Blood: Pathogens	Therapy
92E	Negative	Negative	Negative	Normal	Negative	*Shigella* (8) *	*Staphylococcus aureus* (8)	Blood transfusion (19), Strocillin (10)†
93E	Negative	Negative	Negative	Normal	Negative	Negative	Negative	No drugs given
71E	Negative	Negative	Negative	Normal	Negative	Negative	Negative	No drugs given
84E	Negative	Negative	Negative	Normal	Negative	Negative	Beta hemolytic streptococcus (15)	Lonosol and saline intravenously (12), Strocillin (12)
78E	Negative	Negative	Negative	Normal	*Strongyloides* (12)	Negative	Negative	Lonosol MB‡ and 5% dextrose intravenously (12), Sulfactol (15)
814E	Negative	Negative	Negative	Normal	*Strongyloides* (22)	Negative	*Staphylococcus aureus* (9, 15), Beta hemolytic streptococcus (15), *Paracolon fecalis* (12), *Staphylococcus albus* (22)	Lonosol MB and 5% dextrose intravenously (9, 16), Achromycin (16-18), Amino-plus, lonosol MB and 5% dextrose intravenously (17-18), Sulfactol (18)

*Numbers in parentheses indicate days postirradiation on which organism was first isolated from stool.

†All drugs given intramuscularly unless otherwise indicated.

‡These letters are an integral part of the name of the parenteral fluid containing glucose used.

TABLE IV

Clinical summary for group III

Animal No.	Preirradiation: Stool: Ova and parasites	Preirradiation: Stool: Enteric pathogens	Preirradiation: Blood: Pathogens	Preirradiation: Blood: Hematology	Postirradiation: Stool: Ova and parasites	Postirradiation: Stool: Enteric pathogens	Postirradiation: Blood: Pathogens	Therapy
56E	Negative	Negative	Negative	Normal	Negative	Negative	*Micrococcus* spp. (8)*	Aureomycin orally (9-11), Strocillin† (9-11), Achromycin (10-11), 5% dextrose and saline orally (10-11), Ionosol MB‡ and 5% dextrose intravenously (10), Aminosol and saline intravenously (10)
96E	Negative	Negative	Negative	Normal	Negative	Negative	Negative	Achromycin (13)
80E	Negative	Negative	Negative	Normal	*Strongyloides* (15)	Negative	*Streptococcus viridans* (15)	Achromycin (14-19), Amino-plus, Ionosol MB and 5% dextrose intravenously (18), Ionosol MB, 10% invert sugar and 5% dextrose intravenously (15,16), Amino-plus and 5% dextrose in Ringer's solution intravenously (19)
55E	Negative	Negative	Negative	Normal	Negative	Negative	Negative	Gamma globulin (7-12), Bicillimycin (8-23), Chloromycetin (14-21), Bejectal (15-21), blood transfusion (14)
83E	Negative	Negative	Negative	Normal	*Strongyloides* (15)	Negative	*Micrococcus* spp. (14)	Achromycin (14-19)
125E	Negative	Negative	Negative	Normal	*Strongyloides* (19)	*Salmonella* (11)	Negative	Bicillimycin (12-16), gentian violet orally (27-36), Entromycin (39-41, 62-69)
99E	Negative	Negative	Negative	Normal	*Strongyloides* (22)	*Salmonella* (8)	*Micrococcus* spp. (15)	Furoxone (14-19)
48E	Negative	Negative	Negative	Normal	*Strongyloides* (29)	Negative	Negative	No drugs given

*Numbers in parentheses indicate days postirradiation that symptom was noted or drug administered.

†All drugs given intramuscularly unless otherwise indicated.

‡These letters are an integral part of the name of a class of Abbott parenteral fluids indicating clinical use.

acute anorexia, diarrhea, bloody diarrhea, dehydration, some epilation, and very low body temperature occurring just before death. At the end of the first week, essentially no white cells or platelets were detected in the peripheral blood. The extremely short survival time of the monkeys in group I makes it impossible to plot curves showing data comparable to that of the other groups.

Figure 3 shows the calorie and fluid intake of the animals expressed as the group mean percent of the amount offered. The numbers in parentheses represent the number of animals comprising the group at that time. These data indicate that failure to utilize available fluid is an extremely important factor in maintaining the normal fluid balance, and that the protective drugs do not appreciably alter the situation. Postirradiation anorexia was seen in both groups, but was somewhat less severe in group III and appeared some seven days later than in group II.

Tables V, VI, and VII describe the pathologic findings for groups I, II, and III, respectively. Bone marrow failure and atrophy of lymphoid tissue are consistent findings in all groups. Animal 48E (group III), which lived 618 days after irradiation, actually showed a slightly hypercellular bone marrow with numerous mitotic figures. It is interesting to observe the occurrence of meningitis (99E, table VII); this finding has been noted in several animals in other phases of the research (6).

4. DISCUSSION

This is the first experiment at this laboratory in which any protected animal has survived as long as 30 days after being given

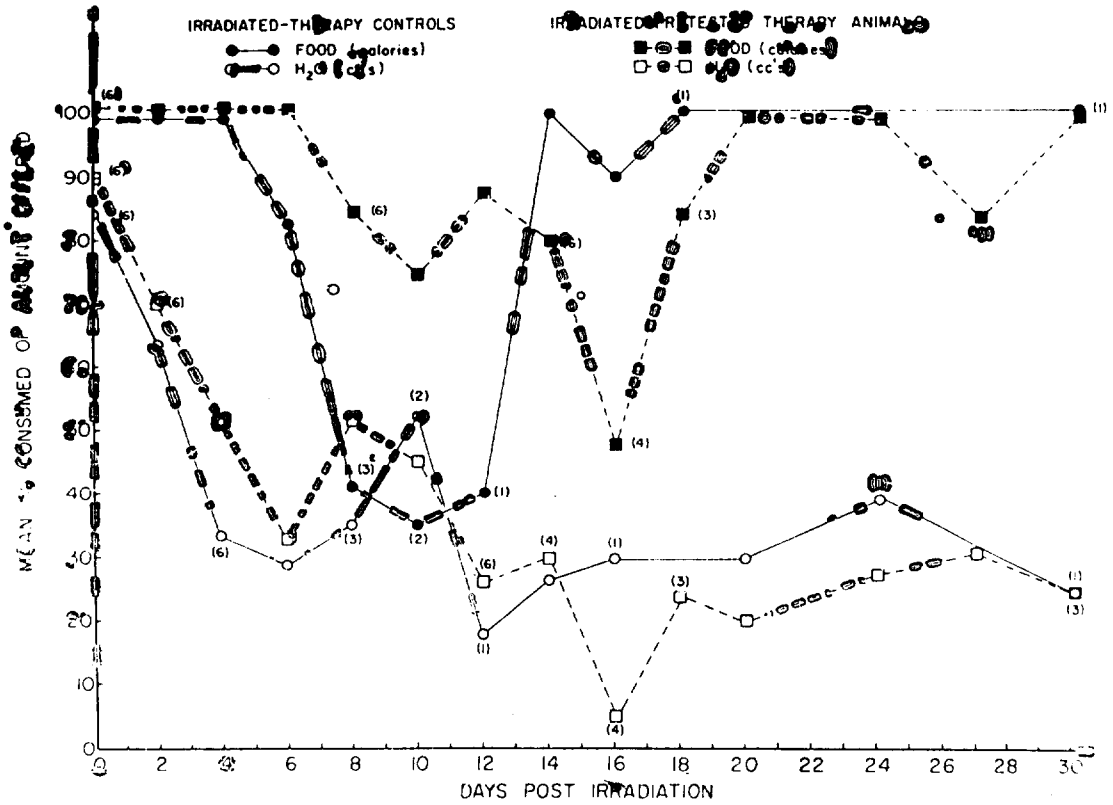

FIGURE 3

Postirradiation changes in food and water consumption for groups II and III.

TABLE V

Pathologic summary for group I

Animal No.	Gross findings	Microscopic findings
115C	Petechiae of skin, stomach. Superficial erosion and hemorrhage, cecum. Focal hemorrhage, colon.	Atrophy, bone marrow lymphoid tissue. Atrophy, slight, intestinal epithelium.
134F	Petechiae of skin. Focal hemorrhage of subarachnoid space, cerebral cortex, lung. Hemorrhagic ulcers, colon.	Atrophy, bone marrow and lymphoid tissue. Slight atypia of colonic mucosa.
74E	Ulceration and hemorrhage, cecum, descending colon and rectum. Petechial hemorrhage, mucosa stomach and urinary bladder.	Atrophy, bone marrow and lymphoid tissue. Fatty metamorphosis, slight, liver.
13H	Petechial hemorrhages of skin, gastrointestinal mucosa, serous surfaces, lungs. Ulceration, mild, colonic mucosa.	Atrophy, bone marrow and lymphoid tissue. Bacterial colonization, kidney, adrenal, and lung.

TABLE VI

Pathologic findings for group II

Animal No.	Gross findings	Microscopic findings
71E	Petechial hemorrhages of skin, serous surfaces, epicardium, stomach, and small intestine. Subarachnoid hemorrhage, focal. Ulceration and hemorrhage, transverse colon.	Hemorrhage and ulceration of colonic mucosa with pseudomembrane formation. Atrophy of bone marrow and lymphoid tissue. Massive hemorrhage and edema of lungs.
78E	Petechial hemorrhages of skin, serous surfaces, epicardium, liver, stomach, colon, urinary bladder. Ulceration and hemorrhage, ileum. Ulceration and hemorrhage, cecum.	Atrophy, bone marrow, with early regeneration. Atrophy, lymphoid tissue.
84E	Petechial hemorrhages of skin, gums, serous surfaces, epicardium, stomach, small intestine, and colon. Hemorrhage and edema, tissues of pelvis. Multiple small hemorrhagic ulcers, colon. Hemorrhage and ulceration, rectum. Severe ulcers, hemorrhagic, skin.	Atrophy, bone marrow and lymphoid tissue. Hemorrhagic ulcers, colon, and skin. Submucosal hemorrhage, focal, colon. Edema, lungs.
92E	Widespread petechial and focal hemorrhage. Focal ulceration of stomach mucosa. Ulcers, lips. Congestion, lungs.	Atrophy, bone marrow and lymphoid tissue. Mucosal necrosis, focal, stomach.
93E	Generalized petechial hemorrhage. Hemorrhage and thickening of colonic mucosa. Subarachnoid hemorrhage, right arachnoid hemorrhage, right frontal lobe, minimal.	Atrophy, bone marrow and lymphoid tissue. Necrosis and hemorrhage, focal, colon.
114E	Softening of right maxilla. Purulent material in maxillary sinus.	Reduced cellularity of bone marrow. Atrophy, lymphoid tissue. Osteomyelitis, maxilla, acute and chronic.

TABLE VII

Pathologic findings for group III

Animal No.	Gross findings	Microscopic findings
55E	Four large perforated ulcers in colon and rectum. Small white nodules throughout lungs. Calcified nodules in spleen. Petechiae of stomach and bladder.	Focal fibrosis and calcification of spleen and lungs. Acute purulent meningitis, cerebellum and cerebrum. Penetrating ulcers of colon. Atrophy, lymphoid tissue. Hypoplasia, myeloid series, bone marrow.
66E	Widespread petechial and focal hemorrhage. Dilatation, stomach and small intestine. Hemorrhagic colitis, cecum. Ulcers, lip.	Ulceration and hemorrhage of colonic mucosa with pseudomembrane. Atrophy, bone marrow and lymphoid tissue. Widespread bacterial colonization.
80E	Subcutaneous hemorrhage and edema, face, and neck. Generalized petechial hemorrhage. Subarachnoid hemorrhage, focal. Hemorrhage and edema, lungs.	Atrophy, lymphoid tissue. Hemorrhage, edema, and pneumonia, lungs. Regeneration, bone marrow.
82E	Edema and congestion, colon, slight.	Crypt abscesses, colon. Atrophy, lymphoid tissue. Hypocellularity of bone marrow.
98E	Hemorrhage, petechial and focal generalized. Hemorrhage, neck and mediastinum. Multiple small white nodules, liver. Hemorrhage and edema, skin, colon.	Atrophy bone marrow and lymphoid tissue. Focal necrosis, liver. Bacterial colonization, generalized. Hemorrhage and edema, submucosal, colon. Focal hemorrhage and pneumonia, lungs.
89E	Hemorrhage, petechial, skin, stomach, rectum, kidneys. Congestion, spleen.	Focal alveolar and tubular necrosis, kidneys. Focal interstitial hemorrhage, kidneys. Thrombosis, focal, glomerular capillaries. Atrophy, lymphoid tissue. Meningitis, acute.
125E	Petechial hemorrhage, heart, small intestine, colon. Hemorrhage, focal, lungs. Multiple small abscesses, lungs.	Mild focal inflammation, colon. Extensive areas of pulmonary edema, hemorrhage and inflammation with abscess formation. Abscess, myocardium.
48E	Congestion, lungs. Mucosal ulceration with pseudomembrane formation, ascending colon.	Slight hyperplasia, bone marrow. Atrophy, lymphoid tissue. Diffuse inflammatory infiltration, lungs. Ulceration and purulent exudate, colon. Hypermegakaryocytosis, focal, testes.

900 r of x-rays. It is also the first time a symptomatically treated animal has survived more than 30 days at this level of irradiation.

The chemical treatment used for radioprotection is more extensive than other treatment previously reported in primates [1, 4]. We combined different mechanisms of protection, routes of administration, and sites and rates of absorption. For example, (1) the intravenous dose affords a high blood level of a good radical sump (AET or a homolog) and an additional compound (cysteine) which may be a radical sump and may also participate in normal oxidative metabolism; (2) an oral dose of the same compounds provides direct physical contact and presumably absorption in the gastrointestinal tract, and allows the total concentration of the drugs to be increased without noticeably increasing the toxicity; and (3) the

use of pentobarbital sodium introduces a drug which decreases respiration (in terms of relative O_2 concentrations), lowers the overall metabolism rate, creates some tissue hypoxia, and potentiates the effect of AET (5).

The actual chemical species present in a homogeneous aqueous mixture of AET and cysteine is yet to be determined. Preliminary work shows that the protective effect of this mixture depends on the concentrations of the two compounds; it also indicates that when the two compounds are mixed in water before treatment, they are more effective than when they are given to the same animal in separate aqueous solutions. The product may be a mixed disulfide or a sulfhydryl compound of relatively high molecular weight. The problem is being investigated by paper chromatographic methods.

There seems to be no question that chemical protection and symptomatic postirradiation therapy can be advantageously combined to ameliorate radiation injury. The chemical prophylaxis very probably decreases radiation damage to the gastrointestinal tract. The fact that it does not appear to protect the lymphoid tissue or the bone marrow confirms the findings already reported in some 80 other chemically protected monkeys that were given lethal or supralethal doses of x-rays (6). These earlier results are further typified by the histopathologic findings that demonstrate bone marrow recovery but lymphatic tissue failure, as in the case of 48E.

The classical symptoms of radiation death—anorexia, diarrhea, dehydration, epilation, and weight loss—are found to a lesser extent, or are delayed considerably, in the therapy animals and in the protected-therapy animals.

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Unclassified Report.

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